Chapter 1

Scientific research and experimenting on human beings

Contents

1.1 Experimentation on human beings

Experimentation is essential in scientific research for the advancement of knowledge.[1] The objective of experimentation is in itself good, insofar as it aims at improving the conditions of man's health and wellbeing, but it must be adequately justified in relation to the protection of the interests and fundamental rights of the subject being experimented on.

The constitutive uncertainty or the incompleteness of knowledge in experimentation (to experiment means 'to verify', 'to test' or 'to put to the test'), the

[1] Starting from the *Nuremberg Code* (1947), through the *Declaration of Helsinki* (1964 and successive revisions) and the drawing up of the guidelines for clinical practice (Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, adopted in 1993 with successive revisions; *Good Clinical Practice* approved by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use in 2002), up to the documents of international and community importance, with different levels of bindingness. In particular the following deserve mention: UNESCO (2005); Council of Europe (1997) and (2004); Regulation of the European Union No. 536/2014 of 16 April 2014 on clinical trials of drugs for human use, which repeals directive 2001/20/EC. In this context see also: European Medicines Agency (EMA) (2016); World Health Organization (WHO) (2002) and (2011).

difficulty in quantifying and foreseeing the possible risks a priori balancing them with respect to the desired benefits, the certainty or probability that the benefits may not be direct on the subject being experimented on but only indirect or also with the only likelihood of benefits, filling this practice with rather problematic elements that require a specific moral and juridical reflection.

Between radical techno-scientism in a libertarian framework that strives for experimentation 'at all costs' and extreme anti-scientism that blocks and hinders all research, in recent years bioethical reflection has consolidated its thought on the limitations of the legitimacy of experimentation on human beings. Even in the context of a moral constitutive pluralism in the bioethical debate that continues to raise theoretical discussions and different practical interpretations, the reflection on the experimentation on human beings has reached some common guidelines at bioethical and biolegal level, making it possible to configure an international and national normative framework of reference.

Notwithstanding a number of distinctions, general shared ethical principles and criteria emerge within such normative framework, considered of specific importance in the experimentation on humans. Such principles and criteria guide the ethical evaluation of scientific research with a binding character in the context of ethics committees for drug trials.

Primarily, the first element concerns the scientific relevance of research and the methodological correctness of the study.[2] The '*rationale*' of the research and the *quality* of the experimentation must be evaluated: if the experimentation is not scientifically valid it is not ethically justifiable. The scientific validity of the study should be considered according to the methodological correctness of the research plan (the statistical consideration of the sample, the analysis of the safety and efficacy phase and the epistemological validity of the methodology adopted), the competence of the investigator, the consideration of the data obtained from the pre-clinical experimentation on animals, the relevance of the results published in the existing scientific literature. Attention should be paid to the scientific justification of the inclusion and exclusion criteria from the research, considering that at times for patients who do not have therapeutic alternatives, the participation in clinical trials constitutes an opportunity from which it would be ethically reprehensible to exclude them.

Secondly, it is essential to make a reasonable evaluation of the proportionality between the likely risks and foreseeable benefits not otherwise obtainable. Every clinical study or experimentation protocol requires an objective consideration of the proportionateness of the risks/benefits ratio. This means that even if a subject were willing to take unreasonable risks, the experimentation could not be authorised at ethical level. It is necessary to bear in mind that the risks are always referred to the subject of the experimentation, while the bene-

[2] On this topics see the Opinions of the Italian Committee for Bioethics (1992), (2009c) (2010b) and (2010c).

fits can directly concern the subject or, much more frequently, indirectly concern the subject and directly the generality of subjects or specific group of subjects who are or will be affected by the same pathology.

The ethical meaning of experimentation is the subject's choice of participation in scientific research, in the uncertainty of the results, with a gesture of solidarity and altruism towards other patients who can possibly and hopefully be treated in the future thanks to the discoveries brought to light by research. A particularly problematic area is represented by the involvement of healthy volunteers in high risk research, with for example exposure to radiation, recourse to electric or transcranial magnetic stimulation.

The ethical need arises to rule out the possibility that the access to experimentation might deprive a patient of the "best therapeutic standard" available. Considering the risks for the subject, the access to experimentation should offer them a better chance with respect to the standard therapy. In this sense non-inferiority trials (with research drugs that are not inferior to the standard therapy) are ethically problematic. Studies should always consist in superiority trials, in the search for a more effective therapeutic outcome than those already existing. Only in this way is a level of safeguard ensured which is at least equal to the one guaranteed by the existing therapy.

This is particularly applicable in the randomisation trials in which the subjects are included randomly in one branch of experimentation or another. It is ethically problematic that in evaluating the effectiveness of a new resource (in a broad sense), the experimentation deprives the recruited subjects of the access to available and validated therapeutic means.

A particularly difficult problem is posed by the use of placebo, or 'fake' medicines. Often proposed by researchers to reduce the time of the trial and to make it more effective and efficient, such method is ethically unacceptable if efficacious treatment is available (of which the subjects would be deprived, for the experimentation) or if the use of placebos entails suffering, lengthening of illness or increased risk. There is wide debate on the ethicality of the frequent recourse to trials with control groups. The possibility is discussed of increasing the retrospective evaluations, improving the filing modality of the clinical data too.

The obtaining of informed consent to experimentation takes on a central ethical role. The informed consent form constitutes a necessary but insufficient element. Informed consent presupposes the information given by means of a dialogue between subject and investigator, suitable for their capacity to understand so as to gain consciousness and awareness of the various aspects of the trial.

At times informed consent is understood in a perspective of defensive medicine, as a detailed technical and exhaustive description of the characteristics of the project (with particular attention to the hypothetical adverse events), aimed at the defence of the investigators rather than of the subjects who have been recruited. Often ethics committees, appointed to evaluate the informed consent

in the context of the analysis of the trials, request a simplification and clarifications of the information modalities, so as to account for the real substiantial and not only formal meaning of consent.

The information and the consent should ascertain the subject's awareness of the meaning of the trial and what their participation entails also in terms of commitment and responsibility, verify their actual willingness without direct or indirect conditionings (the so called undue inducement), vouch for the realisation of the possible risks and potential benefits, as well as the possible consequences of their non-participation (in cases in which there are no therapeutic alternatives), explain the revocability of consent without any consequence in the treatment of the patient and the possible interruption of the experimentation with justified motives on the part of the investigator. Moreover, informed consent clarifies the condition of confidentiality of data and information, explaining the modality to guarantee them and the legal requirements.

An element being debated is the communication of the results obtained during the trial to the recruited subjects, particularly those regarding genetics. Libertarian bioethics considers that the free subjects should decide autonomously whether or not they want to know, even about important information at a preventive, diagnostic, therapeutic level or information regarding reproduction choices.

The bioethics that defends intrinsic human dignity retains that communication is obligatory, except in the case that there might be a conscious refusal on the part of the competent subjects. The obligatoriness should be stressed above all with regard to the parents or guardians, when the information concerns the health of the minors or the incompetent. The communication of "unexpected outcomes" (incidental findings) is particularly problematic, in relation to incurable genetic pathologies with a late onset (for example, Huntington's Corea). In genetic research it is essential to make the subjects aware of the likelihood of such information in order to know their preferences and to arrange suitable genetic consultancies.

Another ethically delicate problem is transparency (except what regards patent profiles) on the results of research, particularly in the case of negative outcomes, and therefore different from the sponsor's expectations. Such results are often not published even though of the utmost importance for future research.

In short, experimentation on human beings is considered licit insofar as the primacy of the interests of human subjects is respected over the progress of scientific research and above all with respect to the economic interests of the market (pharmaceutical companies or industrial sponsors). If carried out properly and in morally acceptable conditions, experimentation on man is not only licit but also dutiful for progress in scientific research. [3]

Even in the framework of a sharing of general ethical principles, particular-

[3] On this topics see Ezekiel J. Emanuel, Christine C. Grady et al. (2011); Council of Europe, Committee on Bioethics (DH-BIO) (2012).

ly thorny elements arise in the bioethical and biojuridical debate in the analysis of a number of conditions of specific vulnerability: minors, women and populations of the developing countries. Such issues need a bioethical reflection and, at times, a compliance and integration of the bioethical reflection on specific points.

1.2 Experimentation on minors

Children are often considered "orphans of therapies". Drugs experimented on adults are often used for children by quantitatively reducing the dosages. In fact, most medicines used to treat children are off-label, that is outside the authorised indications for use and therefore without proper knowledge of the possible side effects in paediatric use. To consider children as "small adults" it not to take into account that the reaction mechanisms of their organism to the taking of the medicine in paediatric age are qualitatively different from those of adults, considering that they are subjects in a development stage. In this sense, the application of the safety and effectiveness data to children of drugs taken from the world of adults exposes them to the risk of inefficacy or adverse reactions. [4]

On the basis of the principle of equality and justice, just like any other human being, children have the right to receive drugs that will guarantee possible conditions of health in the same way as adults do. It would not be ethical to exclude children from trials since it would mean to discriminate against them with respect to other subjects in the safeguard of their interests and fundamental rights such as life and health. Nevertheless, experimentation on minors raises a number of critical ethical and legal issues.

First of all, there is poor recruitment of children in clinical trials. In the methodological planning of a trial it is necessary to take special precautions with respect to experimentation on adults, by virtue of the different age: reduce the

[4] See documents on the topics on an European level: European Medicines Agency (EMA) (2008) and (2012); European Commission (2013); European Commission ad hoc group (2008). The main Opinions on the topics in Europe: Nuffield Council on Bioethics (2015a); U.K. Medical Research Council (2004); Italian Committee for Bioethics (2012); Working Party of Research Ethics Committees in Germany (2010). On an international level: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (2000); International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (2016). In USA: American Academy of Pediatrics – Committee on Bioethics (2016); U.S. National Academy of Sciences (Committee on Clinical Research Involving Children) (2004); U.S. National Academy of Sciences (Committee on Paediatric Studies-Institute of Medicine) (2012); U.S. National Institutes of Health (2016); U.S. Presidential Commission for the Study of Bioethical Issues (2013).

number of medical examinations, guarantee an appropriate reception and recreation spaces, reduce to the minimum invasiveness on the body and discomfort in the experimental procedures that might cause pain, fear and suffering. The low number of samples shouldt also be considered, as it is more difficult to reach the number that is statistically needed to guarantee the reliability of the results (nowadays attempts are made to remedy this problem by creating multicentric networks for each pathology). To this are added the poor economic incentives that reduce the interest of the pharmaceutical companies in sponsoring such research.

In the consideration of the involvement of the lowest possible number of subjects (given the risk), the research should guarantee high scientific and ethical standards in the justification of the importance of the experimentation, in the relevance of measurable results from pre-clinical research on animals and in the analysis of the data gathered from trials on adults, the correctness in being conducted by means of appropriate designs according to the age of the patients, the competence of the investigator, the attention to the detection of side effects or adverse events that take the psycho-physical development of the underage subjects into account.

One of the most critical elements of clinical trials in children is consent. The need to obtain the consent of both parents is a consolidated bioethical line of thought and in particular cases of social hardship (for example, neediness, poor education, immigration) the presence of a cultural mediator from outside the family can be foreseen. It is furthermore important that, with regard to the general information prior to consent, the investigator evaluates the real motivations leading the parents to accept the recruitment of their child in a trial, so as to exclude the existence of ethically unacceptable reasons for this: for example, to benefit from medical treatment otherwise not guaranteed or however to obtain greater attention by the doctors in the treatment of the children.

The consent of the parents should be accompanied by the assent of the child, which is the proof of their actual involvement in the medical decisions, together with their parents. [5] Such assent should be obtained by putting together appropriate information and communication with the child also with the help of psychological and pedagogical studies, suitable for their age and their intellectual and emotive capacity to understand. It is impossible to establish time limits in the formulation of the assent. There should be an approximate separation between pre-school age (with communication by pictures) and early school age (with pictures accompanied by cartoons with short simple explanations), to progressively develop a more complex elaboration up to adolescence or the so-called ‘big minors’. The appropriateness of the information will be evaluated case by case according to cultural and social context but also to the existential context, since each child has a different evolution and maturity and can react differently to illness or pain.

[5] D.S. Wendler (2006), pp. 229–234.

The minor should receive information from expert personnel that is proportional to their capacity to understand the risks and benefits and furthermore the investigator is called upon to take into consideration the desire expressed by the minor to take part in the experimentation or to withdraw from it at any moment. The child should be told that their desires will be considered important in the decision-making, making it clear though that they alone cannot be decisive. Specific attention should be paid so that the involvement of the child is not an indirect insistence on participation, which should always be free and unconditioned by external factors. The conditioning is particularly problematic in a paediatric phase given the child's vulnerability from the external influences of adults, members of the family and doctors.

In the context of assent the child should be helped by doctors to understand the aim of the trial, the procedures foreseen and the experiences that they will have, always attempting to perceive how much the child has actually understood and what their often unexpressed concerns are, in order to help participants to overcome them. It is important that the researchers together with the parents, always act in the best interests of the children, helping them to develop their awareness and choice, whenever possible. In this sense the informed consent/assent cannot be reduced to a mere procedure, but must be carried out in an interaction between doctor, parents and child, to be realized over time so that there is room for clarifications and the reaching of possible shared decisions (the so called shared consent).

Both consent and assent must be in written form. It should be made clear that these records can be withdrawn at any time, without having to give any justification. In the case of conflicts and disputes, suitable psychological assistance and ethical consultation need to be guaranteed. The most delicate part of the assent of children is that of avoiding the imposition of the decision on those who are not able to decide or express a decision for themselves, but also the exclusion from the decision of those who are ready and eager to be involved.

A particularly difficult element is the involvement of healthy or sick children as a control group or as subjects of "non-therapeutic"[6] experimentation, without any direct benefit but only indirect benefit, that is possible benefit for other children in the future with the same pathology.

Non-therapeutic experimentation on minors cannot be excluded, if significant improvements in scientific knowledge were to be achieved from this in the face of a positive will and minimum risk and/or discomfort. The restriction of experimentation to the condition of the existence of a "direct benefit", even though justified by virtue of the protection of the minor, could preclude some therapeutic possibilities specifically devoted to minors. In the measure in which research is essential to confirm data gathered in clinical trials on persons able to give their informed consent or in the measure in which research is such

[6] V.A. Miller and R.M. Nelson (2006), pp. S25–S30.

as to be able to be undertaken only on minors in the absence of experimental alternatives, it can be considered bioethically acceptable. The condition is that the research directly concerns a clinical state that the minor suffers from and which therefore could benefit groups of patients with the same pathology.

In this context it is indispensable that a real capacity of informed assent/ consent exists to the risk and the entity of the risk. When it comes to a non-therapeutic trial on a child with real capacity of informed assent, supported by the consent of the parents/legal representatives, provided that there are no outstanding risks either for the life or the physical integrity of the minor, the bioethical and biojuridical reflection has reached the consideration of the legitimacy of such experimentation. The requisite of the minimum reduction of risk and or discomfort is ethically central to this. Some studies show that young boys and girls/adolescents are motived in taking part even in non-therapeutic clinical trials out of their desire to help others. In the case of subjects who are unable to give consent/assent, non-therapeutic experimentation should be considered morally unacceptable. [7]

There is a different bioethical and biojuridical evaluation regarding the use of experimental drugs as a last resort in the attempt to save the life of the minor in incurable terminal conditions (maybe also in condition of imminence of death) and in the absence of effective therapeutic alternatives.

In such case the ethical decision should be proportionate to the actual circumstances, in order to seek the conditions that are respectful of the dignity of the minor insofar as a human being. In first place, it is essential to gather objective scientific data, in reference to the evaluation of the seriousness of the ill-

[7] The regulation on international level: UN Convention of the Rights of the Child, 1989; Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, 1997; Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research, 2005. Regulation on European level*:* Charter of Fundamental Rights of European Union, 2000 (2000/C 364/01); Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data; Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use; Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance); Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance); Regulation (EU) 679/2016 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation); European Parliament Resolution of 15 December 2016 on the regulation on paediatric medicines (2016/2902(RSP)).

ness (verification of the condition of impossibility to cure him/her), and secondly the present and foreseeably future suffering should be considered, also taking into account the patient's quality of life.

Those experimental pharmacological interventions which are even aggressive and intensive are considered ethically licit and proper when there is an albeit minimum "therapeutic hope" and when the likely suffering is considered acceptable for the benefits that can foreseeably be gained in relation to the improvement of the quality of life (or at least minimization of suffering), with the consent of the parents and possibly the assent of the minors. The suspension of aggressive and intensive experimental therapies is considered ethically licit and sometimes dutiful, when the life expectancy is short, the prognosis undoubtedly poor and the therapies futile and harmful with respect to the benefits to be obtained. In these cases, only ordinary treatment is given along with palliative care and human caregiving.

The use of pharmacological therapies made available by more advanced medicine also in the experimental phase must thus be evaluated case by case during the evolution of the pathology. They are to be considered optional in the absence of other remedies, when, even though not resolutive, they make it possible to alleviate suffering and improve the quality of life even temporarily, with the consent of the parents and possibly the assent of the child. It is also licit to interrupt them, limiting the treatment to ordinary therapy, if they do not give results or if the results fall short of the expectations, presenting high risks and costs in terms of suffering (following medical opinion and the family's consent). In these cases the forced extension of treatment would be uncertain and distressing, thus becoming "therapeutic insistence or obstinacy" or better, "experimental insistence or obstinacy".

1.3 Experimentation on women

As well as minors, sexual difference also brings out other profiles of vulnerability which are peculiar to clinical trials.[8] Women appear as "weak subjects",

[8] While in 1977 the Food and Drug Administration (FDA) in its *General Considerations for the Clinical Evaluation of Drugs* and in 1982 the World Health Organisation in its *Proposed International Guidelines* recommended the exclusion of women from experimentations, it is in 1988 that the FDA in its *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Application* recommends the analysis of data differentiated according to sex in clinical trials. In 1993 once again the Food and Drug Administration issues the *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*, expressing the hope for the inclusion of women in the experimentation protocols so as to guarantee an equal representation. Along the same line are the *International Ethical Guidelines for Biomedical Research In-*

in as much that they are not adequately considered in reference to their specificity. [9]

If female pathologies are excluded, the percentage of women enrolled in the trials is low. One can speak of 'representative inappropriateness' or 'female underrepresentation' in trials. [10] The yardstick for the dosage of drugs is referred to men and women are considered a 'variation' of such model, but the physical, morphological and physiological difference between men and women determines a notable diversity in pharmacokinetics (or in the different absorption, distribution and metabolization of the drug) and in pharmacodynamics (or in the different concentration of the drug in the blood and tissues).

Despite the fact that scientific knowledge of the peculiarity of the female body has made progress, the trial protocols have not been modified with respect to gender difference, with the persisting of nonseparated enrolment with respect to the male and female difference, with the consequent undifferentiated data analysis. The lack of specific studies on women, above all in the early stages of research, does not make it possible to measure the real effectiveness of drugs on them, but could also have limited the identification of specific medicines for women.

The lack of experimental studies that take into account gender difference in the pharmacological field is still even more problematic owing to the recent change in conditions of health/illness of women in the context of the general shift in the female condition, due to the rise in the level of education and in the participation in the working world as well as in the political-social context, but the still ongoing marginalisation. Some of the illnesses considered 'male' today tend to be more frequent in women, but the drugs for their treatment are not experimented specifically on women. This is somewhat penalising for women who are greater consumers of drugs than men, as they have more frequent and serious side effects. Consequently women, who live longer than men, have less health.

There are different reasons for female underrepresentation and numerical inferiority of participation of women in clinical trials. There are reasons that generally concern the way of considering experimentation and medicine. In experimentation there is a tendency towards 'generalisation' and in medicine a tendency towards 'neutrality' and to the assimilation of women to men; but these orientations are in conflict with the need for individual specification and gender differentiation.

Moreover, there are social reasons due to the difficulties of women to get

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volving Human Subjects (1993, revised in 2002), which recommend researchers, sponsors and ethics committees to not exclude women of child bearing age from experimentation, not considering the potential of pregnancy a sufficient reason to limit their participation and recognising women the capacity to take a "rational decision" in taking part in research.

[9] T.M. Wizemann and M.L. Pardue (2001); D.R. Mattison (2004), pp. 112–117.

[10] F. Franconi, S. Brunelleschi, L. Steardo and G. Cuomo (2007), pp. 81–97.

into clinical trials owing to their lack of time (family commitment or the double work-home commitment) or due to low income (unemployment or low salary); psychological reasons due to the lack of attention by the recruiters to practicalities and female needs; environmental reasons owing to lifestyle, the more frequent recourse by women to the use of natural remedies that can affect the experimentation; economic reasons as it is not 'convenient' in terms of costs for the pharmaceutical companies to fund experimentation that needs an increase in enrolments in the preclinical and clinical phase, with the inevitable rise in time and costs; biological reasons as women are considered 'difficult' subjects by virtue of their physiological, enzymatic and hormonal diversity, due to the variations of childbearing and nonchildbearing age. The possible pregnancy in childbearing age is one of the reasons that has led the pharmaceutical companies to exclude women from clinical protocols or to impose the use of specific hormonal contraceptives as a condition for the participation in research because of the possible risks to the foetus.

Bioethical literature is divided on this last point. Some lines of thought, of liberal and libertarian feminism, consider that fertile and childbearing women must be included in the experimentation as a priority ethical need for the potential benefits for women, retaining the possible harm to the foetus as secondary as it is considered as not yet having dignity (at least in the strong sense). [11] The exclusion of fertile and childbearing women from clinical trials would produce injustice in biomedical research, insofar as women would not have the same chances as men in treatment.

In contraposition to this line of thought, the justification of the defence of the intrinsic dignity of human beings from conception leads to a different consideration in relation to female clinical trials. In the measure in which clinical trials can endanger the life or health of the foetus recognised as the subject of rights, the non-participation of women in clinical trials is considered ethically preferable as the risk for the growing life exceeds the potential benefits for the woman. If the woman decided to enrol in the trial for social or personal aims, she should nevertheless be able to choose the modalities freely and responsibly to avoid pregnancy coinciding with her own lifestyle and values, among which abstinence from sexual relations, insofar as she should deem the use of contraceptives illicit owing to the scission between unitive act and procreation (as in the Catholic perspective).

As a counterweight to such theoretical contraposition is a third line of thought, according to which following the awareness of the problems by means of suitable information given during the consultancy, the woman could decide to take part in a trial even if the pharmaceutical company requests the use of contraceptives for safety reasons. Provided that they are not potential early

[11] This is the theory maintained by feminists. Cfr. D.A. DeBruin (1994), pp. 117–146; S. Sherwin, (1994), pp. 533–538 and (1992), pp. 158–175; V. Merton (1996).

abortifacients, the use of contraceptives would be justifiable in the context of an experimental objective (with the intention to take part in a trial and not to avoid conception), also for those who consider the use of contraceptives ethically illicit. In this case the use of contraceptives would not have the aim to separate sexuality and procreation in order to avoid the latter, but only to guarantee the conditions of safety required in the trial, without it entailing the modification of values or behaviour. In other words, a woman who is even against the principle of the use of contraceptives and considers that sexuality is aimed at procreation could use them if requested by the trial without changing her behaviour (that is, practicing abstinence for non-procreative ends). After all, the use of contraceptives can have a therapeutic aim (for example, for the regulation of the menstrual cycle): by analogy it could have an experimental aim (in the case of the study of the interaction between drugs and contraceptives or however to guarantee safety, as it is always possible for the woman to have a sexual union unintentionally, by rape for example).

This is a particularly thorny issue that requires a bioethical debate that manages to balance the needs of the trial on the one hand and on the other the values of the subjects taking part in the experimentation. It is therefore bioethically important that the informed consent is always structured by taking into account gender difference and the moral principles of those taking part in the trials, offering women also sexual abstinence among the possible choices and, should that be impossible owing to trial requirements, offering appropriate consultancy so that women can choose responsibly according to their moral and religious values. It is also important to remember that informed consent must also be undersigned by the partner and can include a variable time frame that can be extended even after the trial.

For the purpose of stimulating the awareness of women and increasing differentiated pharmacological experimentation by sex (experimentation on men and women), it could be important to state specifically on the leaflets of medicines whether or not they were experimented on women. It would also be advisable to raise awareness in the healthcare authorities and pharmaceutical companies to support trials separated by sex, even if not very profitable, encouraging research projects on the subject and promoting the participation of women in clinical trials with adequate information on the social importance of female experimentation. A possible proposal also consists in a greater presence of women as investigators and as members of ethics committees, as they are more sensitive to female issues in clinical trials. In this sense, it would be advisable to have healthcare training that focuses on the female dimension of pharmacological experimentation, as well as research and treatment. [12]

[12] On the topics see the Opinion of the National Ethics Council in Europe: Austrian Bioethics Commission at the Federal Chancellery (2009); Belgian Advisory Committee on Bioethics (2004) and (2015) on the Ethical Implications of the "Statute" of the Pregnant Partner of a Male Partici-

A specific bioethical issue in female clinical research involves pregnant women. In this context, physicians often prescribe drugs for pregnant and breastfeeding women, without studies involving women in those conditions, so without evidence of safety and efficacy. Such treatments include medications that may have a serious harm both to the woman and to the foetus. The exclusion of pregnant women from clinical trials is the cause of the lack of data on potential benefits and harms on them and their future children. Therefore, there is a discussion on the necessity to design research for pregnant and breastfeeding women in order to verify unknown risks and potential individual benefits. [13]

Clinical research on pregnant women needs specific ethical requirements: research that may or may not have a potential direct benefit is allowed only when studies cannot be carried out on other persons, non pregnant and non breastfeeding women; for research with potential direct benefit on the subjects, the risk-benefit assessment must consider the specific situation of pregnancy, and extends assessment on the foetuses or even preconceptional stage. In such research the criteria of minimal risk and minimum burden are compulsory both for the woman and the child. The issue of "minimal risk" refers to the degree of harm or discomfort which should not be greater than those experienced in daily life or during routine physical or psychological examinations. A specific attention and prudence is required by research ethics committees. In any case, relying on evidence from prior animal experimentation is absolutely necessary.

Pregnant or breastfeeding women should not participate in non-therapeutic research that carries more than minimal risk to them and to the foetus or infant, unless this is intended to elucidate problems of pregnancy or lactation without any alternative paths.

When a pregnancy has been exposed to more than minimal risk in the conduct of research, the woman should be encouraged to participate in any available follow-up evaluations to assess the effect on her and her foetus or child.

As part of the informed consent, the woman should be informed of all types of risks of the participation, with specific consideration for the implication on

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pant in a Clinical Trial; European Medicines Agency (EMA) (2005a) and (2005b); Italian National Bioethics Committee (2008). In USA: Columbia University Institutional Review Board (2012); John Hopkins University Center for Communication Programs (2003); The American College of Obstetricians and Gynecologists (2015); The Society for Women's Health Research – United States Food and Drugs Administration Office of Women's Health (2011); U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Office of Research on Women's Health (2011); U.S. Government Accountability Office (1992); U.S. Government Accountability Office (2001); U.S. Food and Drug Administration (1993); U.S. National Institute of Health (2001). In other countries and on international level: Health Canada (2013); International Conference on Harmonisation (ICH) 2004; World Health Organization (WHO) (1995), (1998) and (2010).

[13] CIOMS 2016, Commentary on Guideline 19.

her health and on the embryo, foetuses, infant. If new scientific information arises during the research, this information should be immediately given to participants as soon as possible. As at any stage of the research, subjects' right to withdraw consent should be respected.

Follow-up of the pregnancy, foetus and child is essential, even for several months after the end of the study.

Research on pathological conditions or treatments specifically aimed at the foetus may equally be the focus of research studies. The primary goal of these interventions is to improve the health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities. This leads to consequences for the woman's health and bodily integrity, so it cannot be carried out without her explicit consent.

1.4 Experimentation in developing Countries

The globalization of research would increase the conditions of justice and equality in the distribution of drugs. Although the globalization of clinical studies hides, often, the objective of 'outsourcing' the experimentation, in order to reduce costs, simplify and accelerate procedures. The reference is to the experimentations that involves those populations that are particularly 'vulnerable' mainly because of economic underdevelopment that slows down the progress of science and technology or, even if economically developed, unaware of ethical issues. These conditions may expose some populations to a risk of exploitation for scientific interests, which may hide commercial interests. It may be considered as a form of bioethical 'colonialism' and 'imperialism' (or, in a moderate expression, 'paternalism'), unfair exploitation and manipulation due to the differences in scientific-technological knowledge and socio-economic and cultural inequalities.

The general ethical standards which must be considered mandatory, as substantive ethical requirements for clinical trials on international level are: the protection of all human subjects regardless of ethnical belonging, culture, religion, socio-economic status, country of birth or residence and the guarantee of the conditions of justice, respect of equality (in the equal access to health) and of different cultural contexts.

The respect of dignity, physical integrity, autonomy of participants and justice between subjects in accordance to the good clinical practices are ensured through: preliminary verification of scientific relevance of research; protection of safety and well-being of participants; equity in the enrolling and selection of participants; balance of reasonable risks compared to potential benefits; expression of informed consent; appropriate treatment during and after the trial;

compensation for direct damages to health; distribution of equal burdens and benefits.

The application of general ethical standards of clinical trials to the different cultural context, in particular to developing countries, needs an activity of interpretation and specification. In an ethical framework that recognises the priority of the human dignity and justice emerges the necessity of additional standards of safeguard to avoid exploitation or abuse of particularly vulnerable population because of poverty, lack of education and understanding of scientific issues, lack of technical skills, scarce resources, disease, inability to have access to the most basic and essential health products and services. [14]

The process of interpretation might be helped by a community consultation to acquire better knowledge of local culture and involving community representatives in the elaboration of research projects. In this context, the role of the cultural mediator is important. The aim is neither to impose foreign ethical standards nor to adapt to local standards, but to apply generally recognised principles and values taking seriously into account the conditions and needs of the specific culture.

The *Universal Declaration on Bioethics and Human Rights* of UNESCO (2005) constitutes a reference point for the protection of human beings in transnational research, in order to avoid economic interests prevailing over respect of dignity, autonomy and justice. There is a need for Western Countries to realise that advances in scientific knowledge do not mean that thay can use them to exploit poor countries for one-way benefit. The intrinsic value of this obligation should be the same for each country and ensure that each country may benefit from the positive results of clinical trials regardless of the level of literacy, wealth, social advancement, techno-scientific progress. This is one of the concrete paths to deliver global justice in health and welfare.

The *Universal Declaration on Bioethics and Human Rights* of UNESCO expresses the general framework of reflection with references to human dignity (Article 3), the direct and indirect benefits for patients participating in the research (Article 4), informed consent (Article 6), respect for human vulnerability and personal integrity (Article 8), equality, justice and equity (Article 10), non-discrimination (Article 11), respect for cultural diversity (Article 12), solidarity and cooperation (Article 13), social responsibility and health as a fundamental human right (Article 14), international cooperation (Article 24), promoting the international dissemination of scientific information, freedom of

[14] On the topics see: French National Consultative Ethics Committee for Health and Life Sciences (2003c); Italian Committee for Bioethics (2011) and (2017b); European Group on Ethics in Science and New Technologies (EGE) (2003); Nuffield Council on Bioethics (2005); U.S. Food and Drug Administration (2013) and (2016); U.S. National Bioethics Advisory Commission (2001); U.S. National Institute of Health (2001); P. Marshall (2007); M.P. Neves (2009); UNESCO (2008), (2013) and (2015).

movement and sharing of scientific and technological knowledge.

The Declaration recalls the general ethical principles of experimentation on human subjects, recognized in international documents, affirming that they should be applicable everywhere, without making a distinction between more or less developed countries, avoiding unequal treatment and recognizing the universal justice. This does not mean accepting a 'double standard' of ethics (also called 'ethics dumping'). On the contrary, it means reiterating that the ethical standard should be 'unique' as concerns principles. Trials in developing countries must meet the same ethical standards of developed countries (Article 21 b).

The specific additional standards ethically required, explicitly or implicitly, are the following: direct relevance of the clinical trial, equity in enrollment, tailored informed consent, proportionality and compensation for risks/damages, training and assistance in order to develop a 'collaborative partnership'.

Responsiveness and direct relevance of the clinical trial to real health needs is a specific requirement with regard to the vulnerable population of the host country. International testing should be considered as a priority in relation to the specific interests and priorities of health of the populations of the host country. In this sense, the right to health care as protection of the objective good of a person must be considered a fundamental international right.

Enrollment of the subjects should guarantee equity considering the possible advantages of participants in relation to the population and ensuring benefits both to participants and to the population as a whole. The balancing of risks / benefits should be commensurate with the basic conditions of the population (including nutritional, epidemiological and health conditions), in reference to each individual, but also to the community. Commensuration of risk for the individual and the population in relation to the benefits for 'third parties' (with reference to the Countries performing the trials) is ethically unacceptable. Research is ethically justified if it provides reasonably direct benefits to participants and indirect benefits for the overall population, with the minimization of risks to people participating in the research, but also for the vulnerable population as a whole.

Informed consent should be tailored to local customs, verifying that it is voluntary and freely given without coercion, incentives or 'undue inducement'. It may be oral and witnessed for the illiterate, with permission of community leader or family involvement when needed in specific circumstances. With regard to voluntariness and lack of 'undue' influence, it should be noted that in developing Countries participation in a trial could be an advantage for those who have difficulty in obtaining food and basic health care. The socio-economic conditions could push to participate without an adequate awareness of the risks in the research.

Another problem could be the difficulty of some populations to grasp the concept of research, which tends to be confused with care and assistance (the so

called ‘therapeutic misconception’). The involvement of other persons in the expression of informed consent is acceptable only if there are ways to verify the actual awareness of individual participation (as well as the possibility to withdraw it) and the absence of direct or indirect external pressure. This awareness should be verified as being personal and cannot be replaced by others.

An issue connected to informed consent is confidentiality. Confidentiality may be weakened (if not obliterated) given the family’s possible involvement in the process of granting permission to carry out research. The fact that in some cultures there is a lack of the concept of ‘privacy’ should also be considered. This raises an ethical problem: the participation in research may mean, for vulnerable populations, the risk of the stigma of being sick. In this context, cultural associations may play a supportive role, helping the patient not to be marginalized.

Appropriate treatment should be guaranteed, ensuring that participants enjoy potential benefits and is compensated for any harm directly related to participation, helping health care infrastructure to support proper distribution and guaranteeing continued access to post-trial benefits and treatment to participants and to the population outside the research context of the country where the trial is conducted, as expression of international cooperation and solidarity. This means also that protection should be provided through arrangements a mandatory insurance in view of possible damages, where the premium is assessed in relation to the local economic state. This could be guaranteed also by independent organizations that are non-profit and internationally accredited, which may have the role of monitoring this ethical requirement.

An ethical requirement is the need to assist developing Countries in building the capacity to become fuller partners in international research both on scientific and ethical levels, enhancing collaboration and creating an atmosphere of trust and respect. Assistance should be guaranteed to developing Countries during the experimentation without inflicting on them the burden of the ‘indirect costs’ of the trial, on an already precarious local health system, and helping them to become full partners in international research, stimulating the improvement of the local health system and transferring technical and scientific skills, involving also doctors and representatives of the host Country, to monitor compliance with ethical standards and avoid abuse.

It is an ethical requirement of experimentation that the investigators assume responsibility and solidarity in the framework of international cooperation which continues even after the trial, so that research participants do not feel abandoned. In this sense, experimentation is justified to the extent that the product, if it proves effective, can become available to the entire population. There is considerable international debate, even as regards the ways in which this ethical requirement can actually be met.

There should also be specific training for doctors and the medical staff con-

ducting this experimentation as well as education involving local doctors and health personnel, often in particularly fragile conditions, so that care becomes a 'collaborative partnership' and enables to develop in the host Country the skills required to independently conduct clinical trials and ethical assessments (also, possibly, with the institution of Ethical local Committees). [15]

1.5 Unexperimented drugs and compassionate care

There is wide debate in bioethics on the limits of legitimacy of the use of drugs or technologies that are unexperimented or being experimented for their effectiveness and safety. [16] This is an issue that arises in the debate sparked by 'cases' that attract the attention of public opinion, as happened with some oncological treatments (cures for oncological patients made up of a mix of off-label drugs, or used outside medical prescription, with different indications, dosage and modalities) and the case of the taking of mesenchymal stem cells present in bone marrow, with variable combinations, proposed to treat a range of heterogeneous illnesses, associated by the absence of effective remedies offered by medical science and poor prognosis.

The move towards the use of drugs with unauthorised unexperimented treatments is on the rise, the so called 'early access' to innovative treatments, unproven (alternative medicines) or not yet proven. Such cases have also led to social conflicts, with the claim of the right to treatment by patients and families to the national healthcare system, which has involved the intervention of judges. This is an issue with international dimensions.

Generally in bioethics the generic expression "compassionate use" is employed for a plurality of cases, having in common the will/request/desire to use unexperimented drugs or technologies. The request for compassionate use arises from a number of factors: on the one hand from the slowness and rigidity of the experimentation procedures (slowness, proceduralisation and rigorousness are also a guarantee of precision) and authorisation for the marketing of the drug by the regulatory authorities; on the other hand, from the increase in

[15] In the context of international guidelines the ethical criteria of experimentation with particular reference to developing Countries have been developed (*International Ethical Guidelines for Biomedical Research Involving Human Subjects* 2002, which updated the 1993 guidelines of the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization; *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects,* in its most recently developed form by the World Medical Association (adopted in 1964, revised in 1975, 1983, 1989, 1996, 2000 and 2008)[15], Working Party for the Elaboration of *Guides for Research Ethics Committee Members* (CDBI, 2010, Rev. 1. 2).

[16] Italian Committee for Bioethics (1992).

knowledge, also through the information and communication technologies, of the patients and family members that come to know about new products that have still not been validated and, in the tragic nature of the condition of the illness, do not want to leave any stone unturned. In the age of techno-scientific progress death and illness are even less accepted, and one tries to do everything possible to recover and get better. This is out of an excess of trust in science and medicine, but at times out of a mistrust for 'traditional' medicine, preferring innovative and yet still unvalidated channels.

It is necessary to distinguish between the compassionate use of drugs and the so-called "alternative medicines" or complementary medicines that concern the practices whose effectiveness has not been ascertained with the criteria adopted by scientific medicine and is not "ascertainable". Instead, compassionate use regards cures and treatments not yet ascertained de facto but ascertainable in principle, on the basis of the experimentation procedures. This is often the condition of patients with rare pathologies which, owing to the time and costs of the treatment, have no drugs (the so-called "orphan drugs" or "orphan diseases"). Many patients with rare pathologies do not therefore have courses of treatment and there are very few medical experts able to accept them as patients.

The requests for "compassionate use" pose many questions in bioethics. To what extent does a right to the freedom of treatment, a right to hope exist? When does the hope become illusion, with negative consequences on the health of the patient and for the whole society? [17]

In order to give an answer to these questions it is essential to make some preliminary distinctions. The formulation "compassionate use" groups together different types of situations in a shade of intensity, from the minimum to the maximum: the use of off-label drugs (outside prescription for indications, dosage and directions for use, but validated for effectiveness, safety and tolerability) to the use of unvalidated drugs undergoing validation (early access, in controlled conditions), to the use of drugs without validation (of which not even the absence of harmfulness is known).

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[17] See art. 37 of the *Declaration of Helsinki* (updated in October 2013) that provides for the possibility of "unproven interventions in clinical practice". It allows the use, under the responsibility of the doctor and with the consent of the patient or his legal representative, of "an unproven intervention", when there are no proven treatments or other known interventions have proved ineffective, and after seeking expert opinion on the subject. The doctor must be convinced that this drug could "constitute a hope to save the life, restore the physical integrity or alleviate the suffering of the patient". The article adds that "this intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and made publicly available when appropriate". In one of the many drafts of the Universal *Declaration on Bioethics and Human Rights* of UNESCO, art. 16 of *Scientific and Rational Method*, after pointing out that every decision and practice should be based on the best scientific information available, stressed that (v) "be considered individually, allowing for the possibility of exceptions to general rules and practices". The article was then removed from the final version, but it is the sign of a debate within the international community itself.

In the first case the risks are sufficiently controlled: it is the case that generally arises for the use of drugs on children which have been experimented on adults. In the second case the risk margin and uncertainty increases, as the clinical trial process has not been concluded. The latter is the most problematic case since no data exists even on the harmfulness of the drug: it is the case of the "journeys of hope" for cell therapies, in the case of diseases with a poor prognosis. Another one is the "Ebola case", a disease that per se is rare but to which is added the danger of contagion and rapid spread (pandemic), which can transform it into an epidemic with high levels of mortality, making it more urgent to try and find a solution, not only in the interest of the single individual but also of the community: [18] in this case the risk and uncertainty must be balanced with the benefit for the whole society as well as for the single person.

Moreover, the very expression "compassionate" is ambiguous. It evokes feelings of compassion, empathy towards patients with serious and incurable illnesses which implicitly presuppose the ethical legitimacy: who could be opposed to feelings of empathy, without being considered indifferent or selfish? These are alternative expressions proposed, in order to avoid this ambiguity, as the expression "non-validated treatments for personal and non-repetitive use", which covers the elements common to the different typologies described. These are exceptional treatments, to which it is possible to guarantee access to patients in the absence of validated alternative therapies, in serious cases of urgency and emergency in life threatening cases, when the existing therapies have been ineffective (both in relation to recovery and improvement of quality of life, but have rather worsened the condition).

Access should however be subordinate to a reasonable, robust and solid scientific basis, with data published in international journals, with scientific evidence at least on animal models and possibly with the results of phase I clinical trials. The prescription for these lies with committee of experts (with the evaluation of the ethics committee of the clinic practice, even if non-binding), designated by public healthcare facilities, in conditions of transparency: absence of conflicts of interest, publication both of the composition of the products and the results of the treatment, exhaustive explanation to the patients of the potential dangerousness of non-validated treatments, responsibility for the drugs borne by the manufacturers and monitoring carried out by national healthcare bodies. Only under these conditions can "compassionate" treatments be considered ethically licit and be included in the general right to health.

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[18] 'Expanded access' refers to treatment offered to patients in the absence of other effective treatment, emergency for individual and public health. Nevertheless, the spread of contagion cannot be sufficient to allow compassionate treatment only in these circumstances and thus result as being an advantage for these patients. If one considers the point of view of the person affected by a rare disease, with high mortality but not contagious, the lack of danger of its spread would paradoxically deprive these patients of an opportunity that others instead have in trying a treatment.

The access to unexperimented therapies should not be a 'hidden' or 'fake' trial, which, by means of the compassionate use, obtains results by bypassing the usual long trial procedures. Furthermore, the access to treatments should not be coercive to the extent that, owing to pandemics, there is danger for public health. The right to treatment should always be balanced with the economic sustainability of healthcare and with medical accountability (insofar as it is the doctor that prescribes and administers the drug). Consent must be suitably informed, covering the uncertainties, the limits to hope and possible harmfulness or even lethalness. Risk-taking should always be personal, not substitutable and conscious. [19]

The treatment of minors represents a particularly delicate area, and understandably so if requested by parents who persist in removing the imminence of death of their child. Compassionate practices should never be miraculous illusions but need to be based on scientific reasonableness, so as not to give false hope thus causing even more pain and suffering. Associationism gives important support to families in this sector.

The doctor should be recognised as having the possibility to abstain from prescribing drugs or technologies for compassionate use, insofar as, to the best of his knowledge and his own conscience, he considers them dangerous treatments and too risky for the patient (a sort of "experimental obstinacy"). The right to autonomy and professional deontological responsibility prevail over the possible need to guarantee therapeutic continuity. This is not a case of conscientious objection, since the physician does not find himself before a conflict of values or different views on life, but a case of 'scientific objection' before the respect of those fundamental principles that are at the basis of medical practice.

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[19] The expression "compassionate use" can be traced in art. 83 of EC Regulation no. 726/2004, that authorizes individual states to derogate from the Community rules for the marketing of drugs in the event that a group of patients with a chronic, seriously debilitating or life-threatening illness, cannot be treated satisfactorily with an authorized medicinal product. EC Regulation no. 726/2004 was amended by Regulation no. 1394/2007. The latter introduces for the first time the definition of "advanced therapies", including not only gene therapy and somatic cell therapy, as well as tissue engineered products. The main innovations introduced by the Regulation include: the establishment of an expert committee (Committee for Advanced Therapies), within the European Medicines Agency (EMA); the adoption of new requirements for quality, safety and traceability of the donation, procurement and control; the adoption of new regulatory procedures for classification and certification; support for small and medium businesses with incentives to promote entrepreneurship. In addition, Regulation stipulates that each Member State should standardize the production and use of advanced therapies for individual patients, treated in national public facilities, and therefore not aimed at placing on the market and commercialization.